VII D. Bone, Muscle and Skin

There is a deposition of bone in soft tissues in patients who suffer from carbon monoxide poisoning (Ri, 1966; Mouren et al., 1972). The mechanism for this deposition is not known. In the laboratory, carbon monoxide has been used as a tool to test the polarizing power of bone mineral (Nash and Beebe, 1969).

Some patients suffering from acute carbon monoxide poisoning develop contractures of the skeletal muscle (Howse and Seddon, 1966; Kolb, 1968). Three factors contribute to the development of contracture: (1) ischemia due to reduction in blood oxygen content; (2) hyperexcitability of neuromuscular junction (Paris, 1964); and (3) binding of myoglobin with carbon monoxide (Rossi-Fanelli and Antonini, 1958; Wittenberg et al., 1965; Gladyshevskaia et al., 1966; Coburn and Mayers, 1971; Rudolph et al., 1972).

The cutaneous lesions in a patient with carbon monoxide poisoning are varied. They include bullae, subepidermal vesicles, intracellular edema and occlusion of the epidermal portion of sweat ducts (Jopkiewicz et al., 1965; Long, 1969; Leavell et al., 1969; Ippen and Goerz, 1969; Baden, 1970; Achten et al., 1971). Erythema of the face associated with a cherry-red color of the blood is a classical diagnostic sign of poisoning with carbon monoxide (Danto, 1964).

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D. Bone, Muscle and Skin

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VIII. CARBON MONOXIDE POISONING

It is rather a remote possibility that cigarette smoking may cause death by carbon monoxide poisoning. There are publications on the diagnosis and treatment of carbon monoxide poisoning, both accidental and industrial. The additional bibliography lists relate to the following topics:

Accidental poisoning involving carbon monoxide and other causative factors (no. 14).

Accidental poisoning involving carbon monoxide (no. 15).

Industrial poisoning involving carbon monoxide (no. 16).

Therapy of carbon monoxide poisoning (no. 17).

Therapy of poisoning by use of normobaric and hyperbaric oxygen (no. 18).

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Page			Reprint
116	(1)	Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service, 344-345, 1964.	634
117	(2)	NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH: The health consequences of smoking, 62-64, 1967.	635
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(1) SMOKING AND HEALTH: Report of the Advisory Committee to the Surgeon General of the Public Health Service, 344-5, 1964.

SMOKING AND ACCIDENTS

Smoking has been associated with a variety of accidents. Among these, fires have the most obvious and important consequences.

In a special study of home accident fatalities in 1952 through 1953, the Public Health Service and the National Safety Council reported that 231 (18%) of 1,274 deaths from fires of known origin were due to cigarettes, cigars or pipes (1).

The Metropolitan Life Insurance Company reported that of 352 deaths in 1956 and 1957 among their policyholders from fires and burns with known causes in and about the home, 57 (16%) were due to smoking (2).

Of physiological responses related to driving, smoking degrades detectably only the differential brightness threshold and this effect increases with amount of smoking (4). The epidemiological data available on the effects of smoking on traffic accidents are inconclusive.

It has been shown that a level of carboxyhemoglobin of 5 percent--a level which is not uncommon among heavy cigarette smokers (3, 6)---depresses visual perception to as great an extent as anoxia at 8,000 to 10,000 feet altitude (4, 5).

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(a) The epidemiological data reported by Boeck (1948) indicate that cigarette smoking is not responsible for the occurrence of vehicular accidents and poor driving (see page 37).

(b) A more recent report by Bender et al (1971) states that exposure to 100 ppm carbon monoxide for 2-1/2 hours, with mean blood levels of 7.2% carboxyhemoglobin, diminished visual perception. There was no difference between smokers and nonsmokers with regard to their susceptibility (see page 88).

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(2) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH: The health consequences of smoking, 62-4, 1967.

Carbon Monoxide Effect

The gaseous phase of cigarette smoke contains about 4 percent carbon monoxide. This quantity can increase the levels of carboxyhemoglobin saturation of cigarette smokers from 2 percent to 10 percent (*21*). The average nonsmoker, depending on environmental exposure, usually has less than 2 percent carboxyhemoglobin saturation (*10*). Since smokers of one pack or more a day may have chronically elevated carboxyhemoglobin levels of more than 4 percent (*9*), there may be appreciable differences in the carboxyhemoglobin levels between some heavy cigarette smokers and nonsmokers.

(a) The carboxyhemoglobin blood levels of cigarette smokers expressed as ranging from 2% to 10% is not an accurate statement. A survey of the literature reveals 30 investigations with an overall mean level for 2,054 smokers of 3.76% in the blood taken 4 to 12 hours after smoking. Only 30% of subjects have levels exceeding 5% (see pages 12 to 14). The peak levels after smoking one or more cigarettes had a mean of 5.26% (see page 20). A more accurate statement would be based on integration of levels taken at hourly intervals but such information is not available.

In addition to displacing oxyhemoglobin, carbon monoxide effects a shift in the oxygen-hemoglobin dissociation curve (*2, 3, 4, 5, 6*). This may result in a decreased release of oxygen at the tissue level. A series of studies (*61, 62*) has been performed on young adults to analyze the effect of cigarette smoking on carboxyhemoglobin levels, and the consequent effect on some parameters of cardiopulmonary function. An increased post exercise oxygen debt was observed after cigarette smoking as compared to controls. This, in part, may reflect not only ventilatory disturbances but also a decreased supply of oxygen in the blood due to the carbon monoxide effect, resulting in less available oxygen to meet the increased tissue demand. Similar post-exercise oxygen debts have been noted after inhalation of enough carbon monoxide to produce comparable blood levels of carboxyhemoglobin (*21*).

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(b) Inhalation of carbon monoxide in man, with blood levels of 5% to 10% carboxyhemoglobin does not influence ventilation. Ayres et al (1965) used short-term exposure and Astrup et al (1968) exposure for 8 days (see pages 42 and 45).

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Commentary (2) National Clearinghouse, Cont.

The consequence of the smoking/carbon monoxide effect appears to be especially important in the myocardium where relatively more oxygen is normally extracted from the coronary circulation as compared to other organ systems. (Coronary venous blood usually has an oxygen saturation of less than 25 percent, whereas blood leaving some other organs is about 75 percent saturated with oxygen (45).)

Dogs were exposed to carbon monoxide to elevate their carboxyhemoglobin saturation levels (9). In response to inhalation of carbon monoxide there was an increase in coronary blood flow but a decrease in coronary arterial-venous oxygen differences. Patients with coronary heart disease were also studied following inhalation of enough carbon monoxide to elevate their carboxyhemoglobin saturation levels to the range of 5 to 12 percent (9). In response to carbon monoxide there was generally an increase in the cardiac output and the coronary blood flow in most of the patients. While the systemic arterial-venous oxygen differences varied, either increasing or decreasing, the coronary arterial-venous oxygen differences decreased, indicating a decreased oxygen extraction by the myocardial tissue despite the myocardium's increased demand for oxygen. These decreases in myocardial oxygen extraction are related to increases in the carboxyhemoglobin saturation levels. It was observed that some patients evidently could compensate by increasing their coronary blood flows adequately to supply the myocardial tissue with sufficient oxygen, as indicated by a rise in myocardial oxygen uptake in these individuals. However, the other patients with coronary heart disease, evidently more severe, could not increase their coronary blood flow rate enough to compensate for the decreased oxygen carried by the blood. This latter group of patients, even though they had increased cardiac output, had less significant increases of coronary blood flow than those noted in the first group of patients. The coronary arterial-venous oxygen differences and the myocardial tissue oxygen uptakes both decreased, indicating that the myocardial tissue oxygen demand was not being met entirely.

(c) The experiment cited in the above paragraph specifies an increase in cardiac output with a carboxyhemoglobin value of 5% to 12%. Experiments by Brody and Coburn (1969, 1970) and Klausen et al (1968) did not show an increase in cardiac output following either acute or chronic exposure of human subjects (see page 56). Experiments on animals show myocardial lesions with exposure exceeding 50% carboxyhemoglobin (see page 57).

The reduction in the amount of oxygen available to the myocardial tissue caused by the absorption of carbon monoxide from tobacco smoke may be especially critical in persons with pre-existing coronary heart disease, especially when they cannot significantly increase coronary blood flow to compensate for increased myocardial tissue oxygen demand. The carbon monoxide effect may, in part, contribute to the increased incidence of myocardial infarctions that occur in cigarette smokers. Additional research is needed.

(d) Carbon monoxide does not contribute to the increased incidence of myocardial infarction that occur in cigarette smokers. Haywood et al (1972) could not find a clear-cut relationship between carbon monoxide levels and incidence of acute infarction. De Bias et al (1972) exposed dogs with experimental myocardial infarction to 100 ppm carbon monoxide (14% carboxyhemoglobin) for 14 weeks and did not observe an increase in severity of myocardial hypoxia (see page 61 and 62).

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(3) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH: The health consequences of smoking, 1968 Supplement to the 1967 Public Health Service Review, 38-40, 1968.

Human Myocardial Tissue Function in Relation to Anoxia and to Carbon Monoxide

Likoff, et al. (98) suggest that an oxygen-diffusion impairment or inappropriate oxygen utilization at the myocardial microcirculatory or cellular level could be responsible for the anginal symptoms and ECG signs of apparent myocardial ischemia in the presence of adequate arterial saturation and patent coronary arteries by coronary arteriography. Ayres (4) and Eliot (33) suggest that these mechanisms may be related to the carbon monoxide effect and abnormal hemoglobin function.

In addition to a review of the coronary circulation as related to myocardial ischemia and angina pectoris, Elliott, et al. (35) studied zonal myocardial ischemia (60) by ECG, coronary angiography and regional lactate metabolism in 50 patients with proven coronary heart disease. They found that the ECG findings could be normal even when severe coronary disease was present with myocardial production of lactate. The regional lactate pattern was very helpful in determining the location of myocardial ischemia and significant coronary artery lesions.

In studies of coronary patients exposed to relatively low levels of carbon monoxide, Ayres (4) has reported that myocardial lactate and pyruvate extraction decreased or shifted to actual production, suggesting the presence of anaerobic metabolism. These data support his previous findings noted in the 1967 report that carboxyhemoglobin can interfere with oxygen delivery to the myocardium to the degree that relative myocardial anoxia can occur. The shift to anaerobic cardiac metabolism, which is relatively ineffective as a source of energy, indicates the presence of myocardial anoxia, and should be regarded as a warning sign. In these same experiments Ayres has noted that the myocardial oxygen extraction is decreased in response to carbon monoxide inhalation, and thus has further demonstrated the relationships of carbon monoxide with relative myocardial anoxia and anaerobic myocardial metabolism. The shift to the left of the hemoglobin-oxygen dissociation curve, describing the decreased ability of hemoglobin to release oxygen at the tissue level, is directly related to increased carboxyhemoglobin levels.

The animal experiments of Weissler (156), noted in the previous section, suggest that glucose might possibly help to temporarily prevent myocardial infarction from relative myocardial anoxia, by providing a substrate for anaerobic metabolism. Since myocardial ischemia may be caused not only by complete coronary arterial obstruction, but also by increased myocardial tissue oxygen demand above and beyond available oxygen supply, it would be important to know whether cigarette smokers have more products of anaerobic myocardial metabolism than do nonsmokers.

Eliot (33) has noted apparent hemoglobin abnormalities in patients with signs of myocardial ischemia or acute necrosis, and in smokers as compared to controls. However, he suggests that there are other hemoglobin abnormalities also present besides the well documented carboxyhemoglobin abnormalities associated with the carbon monoxide effect of cigarettes. Some reverted to normal hemoglobin status after stopping smoking.

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Commentary (3) National Clearinghouse, Cont.

Anomalous hemoglobin-oxygen dissociation was noted in "heavy" cigarette smokers (more than one pack per day) without known coronary heart disease. In experiments where the amount of cigarette smoking was controlled, there appeared to be a threshold effect: more than 12 cigarettes per day caused this anomalous dissociation to occur (53). Birnstingl (9) reports finding an increased hemoglobin affinity for oxygen in smokers, which does not appear to be explained solely by the increased carboxyhemoglobin levels in smokers.

Research to further study the interrelationships of carbon monoxide to the myoglobin of heart muscle should be performed because it is possible that carbon monoxide may replace oxymyoglobin with carboxymyoglobin and disturb the oxygen-dissociation phenomena of myoglobin (88, 130, 159). The limitations of blood supply and the high energy output of heart muscle as compared to skeletal muscle may make the myoglobin impairments by carbon monoxide of possible etiologic importance in cigarette smoking and heart disease.

Hydrogen cyanide appears to be rapidly converted to thiocyanates by the body, but the absorption by the lung of cyanide from cigarette smoke might possibly result in higher serum cyanide levels in the coronary arteries than in the systemic circulation. As noted in the 1964 Report, the cyanide ion is capable of stopping cellular respiration abruptly through inactivation of cytochrome oxidase. In sublethal exposures, the cyanide ion is gradually released from its combination with the ferric ion of cytochrome oxidase, converted to thiocyanate ion and excreted in the urine. Thiocyanate blood levels in smokers are three times higher than in nonsmokers and relative differences in urinary excretion are even more pronounced. Cytochrome oxidase is very important in cellular respiration of all body cells. In view of the extremely high myocardial cellular needs for aerobic metabolism, it is possible that the cyanide ion inactivation of cytochrome oxidase also can occur in myocardial cells and be of critical importance, especially in light of other risk factors such as impaired coronary blood flow, the carbon monoxide effect, and the known increases in myocardial tissue oxygen demand caused by the smoking/nicotine-induced catecholamine release. Further research is needed to determine whether or not cyanide ions in concentrations equivalent to those found in cigarette smokers, have a harmful effect on the myocardium, in terms of both acute and chronic exposures.

(a) The statement that . . . relates directly to cigarette smoking is that of Birnstingl is entirely wrong and has completely reversed the meaning intended by that author. In the original publication of Birnstingl, Cole and Hawkins (1967), the increased oxygen affinity of hemoglobin in the blood of smokers could be "almost entirely due to a raised carbon monoxide hemoglobin level". A copy of a summary of the article which appeared in Brit J Surg 54: 615-8, 1967, follows:

> ...thy male subjects over 40 years of age have a ... oxygen affinity which is greater than that of a similar group under this age. This would result in a shift to the left of the oxyhaemoglobin dissociation curve.
>
> Cigarette smokers also have an increased oxygen affinity, but this is almost entirely due to a raised carbon monoxide haemoglobin level.
>
> Patients with Buerger's disease have a normal oxyhaemoglobin dissociation curve, if age and smoking habits are taken into account. Furthermore, their oxyhaemoglobin dissociation does not appear to be more sensitive to the effects of cigarette smoke than normal ...

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(4) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH: The health consequences of smoking, 1969 Supplement to the 1967 Public Health Service Review, 28-9, 1969.

Carbon Monoxide

Several reviews of the pathophysiology of exposure to carbon monoxide (CO) have appeared recently. These are pertinent to the discussion of the relationship of smoking to health, since cigarette smoke contains amounts of CO sufficient to cause a COHb level of 5 to 10 percent in the smoker, depending on the amount smoked and degree of inhalation (*9*, *10*).

Bartlett (*4*) has pointed out that because the absorption of CO from the ambient environment is dependent upon the concentration of CO in the environment as contrasted to that in the blood, smokers with a COHb level of 5 percent will not absorb CO from inspired air unless the concentration of CO in the air exceeds 30 parts per million. However, he also states that because the excretion of CO between cigarettes will be lower in CO polluted air, the smoker will have a higher long-term average COHb level in a polluted environment. Patients with heart disease may be particularly susceptible to the hypoxic burden caused by the presence of COHb.

Goldsmith, et al. (*10*) have stated that for the U.S. urban population, cigarette smoking is probably the most important cause of increased COHb above the endogenous level produced by heme catabolism, followed by automobile exhaust, occupational sources, and home heating and cooking devices, in that order.

Although Dinman (*6*) minimizes the importance of the effect of CO levels of 5 to 10 percent on the myocardium, he states that a shortcoming in his approach is that focal areas of myocardial ischemia are not reflected in the determination of oxygen saturation made from samples of blood taken from the coronary sinus. Such areas of ischemia might be important in initiating fatal arrhythmias. Levels of COHb which decrease further the oxygen supply to the ischemic myocardium might be readily provided by cigarette smoking.

Eliot, et al. (*8*) have reported effects of cigarette smoking on the oxygen affinity of hemaglobin independent of the presence of CO. Their results suggest that cigarette smoking may have both acute and chronic effects on oxygen affinity which differ in direction. The authors caution, however, that the *in vivo* oxygen affinity of hemoglobin may be different from that implied by the static equilibrium data. Further research is in progress.

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(*6*) Dinman, B. D. Pathophysiologic determinants of community air quality standards for carbon monoxide. Journal of Occupational Medicine 10(9): 446–463, September 1968.

(*7*) Dintenfass, L. Blood rheology in pathogenesis of the coronary heart diseases. American Heart Journal 77(1): 130–147, January 1969.

(*8*) Eliot, R. S., Striff, R., Salhany, J. M., Mizukami, H. Personal Communication. April 1969.

(*9*) Goldsmith, J. R. Carbon monoxide. Science 157: 812–844, August 18, 1967.

(*10*) Goldsmith, J. R., Landaw, S. A. Carbon monoxide and human health. Science 162(3860): 1352–1359, December 20, 1968.

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Commentary (4) National Clearinghouse, Cont.

Most of the references cited are review articles which are commented upon under Bartlett (page 153), Goldsmith (page 165), and Dinman (page 160). The only original work referred to is by Eliot et al, which is a personal communication to the National Clearinghouse.

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Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000

(5) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH: The health consequences of smoking. A report to the Surgeon General: 1971. 59-62, 1971.

CARDIOVASCULAR EFFECTS OF CARBON MONOXIDE

Carbon monoxide (CO) is a colorless and odorless gas, low levels of which have significant effects on human and animal physiology which are just now beginning to be understood. According to Wynder and Hoffmann (179), it is present in cigarette smoke in concentrations of approximately 2.9 to 5.1 percent. The concentration of CO in smoke is subject to many factors, among them the type of tobacco and the porosity of cigarette paper. The concentration of CO in smoke has been found to increase significantly toward the last puffs of the cigarette.

(a) This paragraph states the concentration of carbon monoxide in cigarette smoke but omits mentioning the fact that the smoke is diluted with atmospheric air, dead space air and alveolar air.

According to Chevalier, et al. (41), a concentration of approximately 4 percent CO in cigarette smoke will produce alveolar levels of around 0.04 percent which, equilibrated with hemoglobin, result in carboxyhemoglobin (COHb) concentrations of from 3 to 10 percent. A number of investigators have compared COHb levels in smokers and nonsmokers. Goldsmith and Landaw (75) reported the analysis of expired air samples obtained from 3,311 longshoremen. Using a regression analysis, they calculated the concentration of COHb and found that nonsmokers showed levels of 1.2 percent while those smoking over 2 packs per day had levels of 6.8 percent and that smokers of lesser amounts had intermediate levels. Occupational exposure accounted for the mean nonsmokers' level being over 1.0 percent, an unusual finding in comparison with other studies. Kjeldsen (112) interviewed and obtained blood samples from 934 CHD-free smokers and nonsmokers. The mean COHb level for 196 nonsmokers was 0.4 percent while all inhaling smokers had a mean level of 7.3 percent. All 416 cigarette smokers, regardless of inhalation or amount smoked, showed a mean level of 4.0 percent.

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(b) Chevalier et al (1966), cited in the opening paragraph, did not analyze alveolar air. They expressed the opinion that 4% carbon monoxide in cigarette smoke would result in a concentration of 0.04% after dilution. Jongbloed (1939) analyzed the alveolar air of a smoker after the 4th cigarette; the peak level was 0.0031% (see page 19).

The results of Kjeldsen (1969) have been misquoted. The blood level of carboxyhemoglobin in 934 subjects free from coronary heart disease had the following mean value: 0.4% for 196 nonsmokers and 4.2% for 738 smokers. Of the latter group the 121 light smokers had a mean of 2.5%; the moderate smokers one of 4.1% and the heavy smokers one of 5.7%. The figure 7.3% appearing in the paragraph is for atherosclerotic subjects. (Tables from Kjeldsen's paper are reproduced below.)

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Table VI - 11

Smoking cathegory	Carboxyhaemoglobin (sat. per cent)			Serum cholesterol (mg/100 ml)		
	Controls M ± SD	Atherosclerotic subjects M ± SD	Significance	Controls M ± SD	Atherosclerotic subjects M ± SD	Significance
Smokers	4,2 ± 3,1 (738)	7,0 ±3,7 (57)	p <0,001 (t = 5,52)	247 ± 44 (738)	290 ± 33 (57)	p<0,001 (t = 4,89)
Non-smokers	0,4 ± 0,9 (196)	0,5 ± 0,7 (2)	n.s. (t = 0,16)	236 ± 49 (196)	284 ± 56 (2)	p = 0,02 (t = 2,32)

Table VI-11: Average values of carboxyhaemoglobin and serum cholesterol in smokers and non-smokers in the control group and in the group with atherosclerotic cardiovascular diseases.
n.s. = not significant at the 0,05 level.
The number of subjects in each smoking cathegory is given below the means and standard deviations.

Table VI - 12

Smoking cathegory	Carboxyhaemoglobin (sat. per cent)			Serum cholesterol (mg/100 ml)		
	Controls M ± SD	Atherosclerotic subjects M ± SD	Significance	Controls M ± SD	Atherosclerotic subjects M ± SD	Significance
Light smokers	2,5 ± 2,5 (121)	3,7 ± 2,5 (3)	n.s. (t = 0,76)	245 ± 38 (121)	279 ±67 (3)	n.s. (t = 1,45)
Moderate smokers	4,1 ± 3,0 (463)	7,3 ± 3,6 (34)	p <0,001 (t = 4,95)	246 ± 45 (463)	286 ± 50 (34)	p<0,001 (t = 4,52)
Heavy smokers	5,7 ± 3,0 (154)	7,0 ± 4,0 (20)	n.s. (t = 1,45)	253 ± 45 (154)	298 ± 53 (20)	p<0,05 (t = 2,18)

Table VI-12: Average values of carboxyhaemoglobin and serum cholesterol related to intensity of smoking in normal smokers and in smokers with atherosclerotic cardiovascular diseases.
n.s. = not significant at the 0,05 level.
The number of subjects in each smoking cathegory is given below the mean values and standard deviations.

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Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000

Commentary (5) National Clearinghouse, Cont.

c Carbon monoxide has many varied and significant effects on human physiology. An overall review of these effects may be found in a discussion by Lilienthal (127) or more recently in an extensive review by the United States Public Health Service National Air Pollution Control Administration (194). Apart from its effects on respiratory and circulatory function, CO has been found to affect certain central nervous system functions adversely. These effects are probably due to interference by CO with the proper oxygenation and oxidative metabolism of the tissue in question.

CO interferes with oxygen transport in a variety of ways. First, the affinity of hemoglobin for CO is approximately 200 times greater than its affinity for oxygen, and thus CO can easily displace oxygen from hemoglobin. Second, CO shifts the oxyhemoglobin dissociation curve. By increasing the avidity with which oxygen is bound by hemoglobin, CO interferes with O_2 release at the tissue level. This is of greatest importance at the tissue level where the oxygen content of the capillary blood has been reduced to approximately 40 percent saturation. Here the shift can substantially decrease the oxygen tension supplying the tissues.

Third, and of more recent note, is the possible interference by CO with the homeostatic mechanism by which 2, 3-diphosphoglycerate (2, 3-DPG) controls the affinity of hemoglobin for oxygen. Bunn and Jandl (34) have recently reviewed the various experiments concerning this glycolytic intermediate. The question of whether the low levels of CO present in the blood of smokers can affect this homeostasis is presently under investigation (29, 143), and firm conclusions cannot be drawn at this time.

(c) This is an incomplete list of review articles on carbon monoxide. Fifteen others are available (see pages 6 to 10).

d Apart from its effect on hemoglobin affinity, CO appears to induce arterial hypoxemia, and this may act as an additional cause of tissue hypoxia. Ayres, et al. (14, 15) observed unexpectedly that exposure of individuals to CO sufficient to raise their levels of COHb to between 5 and 10 percent was associated with a significant fall in arterial pO_2. Greater fall in venous pO_2 was noted, but this was considered secondary to increased tissue extraction. In a recent article, Brody and Coburn (30) suggested that this COHb-induced arterial hypoxemia was due to the interaction of a number of factors. These authors noted that in the presence of veno-arterial shunts or of an imbalance in the ventilation-perfusion ratio, the shift in the oxyhemoglobin dissociation curve increased the alveolar-arterial O_2 gradient and resulted in arterial hypoxemia. The presence of shunts as small as 2 percent of cardiac output as well as of approximately 10 percent COHb was found to cause an increase in the gradient. Such ventilation-perfusion (V/Q) abnormalities have recently been noted even in asymptomatic smokers (see Chapter on Chronic Obstructive Bronchopulmonary Disease). The increased levels of COHb found in the blood of smokers may interact with these V/Q abnormalities to further decrease available oxygen.

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Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000

Commentary (5) National Clearinghouse, Cont.

In normal individuals, coronary flow can increase to meet the increased oxygen demands of a stressed myocardium (as that under nicotine stimulation), while in individuals with severe CHD coronary flow cannot respond as readily. In such cases, myocardial oxygen extraction must be increased above the almost maximal extraction found at rest. Any interference with arterial oxygen levels or hemoglobin affinity could very well decrease available oxygen supplies below the level required for proper tissue function. That this occurs is suggested by the experiments discussed below.

(d) The studies of Ayres et al (1965, 1969) were performed in a non-steady state. These papers are discussed elsewhere in this commentary (page 148).

Chevalier, et al (47) exposed 10 young nonsmokers to CO concentrations sufficient to induce COHb levels of approximately 4 percent. Taking measurements from blood specimens obtained at cardiac catheterization under resting and exercise conditions, the authors noted that the ratio of oxygen debt to oxygen uptake increased significantly under conditions of increased COHb. According to the investigators this implied that the same work was being done at a greater metabolic cost. These same authors (121, 122) had previously noted similar findings among smokers and observed that cessation of smoking was associated with a significant improvement in oxygen debt accumulation.

(e) The observations of Chevalier et al were made not on blood but on alveolar air analysis. The subjects inhaled 0.5% carbon monoxide, resulting in an indirectly measured blood value of 4% carboxyhemoglobin. There is a serious error here, since other investigators have obtained 25% to 75% carboxyhemoglobin.

More recent work by Ayres, et al. (17) has focused on the difference in response to CO exposure between 7 normals and 4 patients suffering from CHD (proven arteriographically). The induction of a COHb concentration of approximately 9 percent in the normals was followed by an increase in coronary blood flow, a decrease in hemoglobin-oxygen percent extraction and no change in myocardial oxygen consumption, coronary sinus oxygen tension, and lactate and pyruvate extraction ratios. The induction of similar COHb levels in the CHD patients was followed by no change in coronary blood flow, a decrease in the hemoglobin-oxygen extraction ratio, and no change in myocardial oxygen consumption. However, these patients did manifest a decrease in coronary sinus pO_2 as well as a decrease in lactate and pyruvate extraction. The latter measures indicate that the myocardium was functioning under hypoxic conditions. Because the coronary flow could not increase and because the myocardium could not extract O_2 from HbO_2 which was under the influence of CO, coronary sinus oxygen tension decreased to a point which could inactivate certain oxidative enzyme processes. Thus, the myocardial function of persons with CHD may be unable to compensate for the stresses induced by smoking.

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Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000

Commentary (5) National Clearinghouse, Cont.

(f) The comments in paragraph (d) above apply to another publication by Ayres et al (1969). These measurements were taken in a non-steady state after administering 5% carbon monoxide.

c. Although COHb levels resulting from the CO present in the atmosphere during periods of high air pollution are much lower than those due to the inhalation of cigarette smoke, these concentrations of COHb might contribute to the manifestations of CHD. Cohen, et al. (44) studied the case fatality rates for patients admitted to 35 Los Angeles area hospitals with myocardial infarction in relation to atmospheric CO pollution. The authors observed an increased MI case fatality rate in areas of increased pollution, and then only during periods of relatively increased CO pollution.

(g) The opening sentence is a poor comparison. Instead of atmospheric air and cigarette smoke a comparison between blood levels of nonsmokers and smokers would be pertinent. There is also an endogenous source of carbon monoxide.

Subsequent to a report by Cohen et al (1969), Haywood et al (1972) examined patients dying of acute myocardial infarction or diverse diseases. There was no clear-cut relationship between carbon monoxide levels and acute infarction (see page 61).

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Source: https://www.industrydocuments.ucsf.edu/docs/nmnk0000

(6) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH: The health consequences of smoking. A report to the Surgeon General: 1972. 21-3, 121-135, 1972.

CARBON MONOXIDE

c/ Because cigarette smoke contains from 2.7 to 6 percent carbon monoxide (CO), significantly higher carboxyhemoglobin (COHb) levels are found in smokers than nonsmokers (12, 20, 24, 65). COHb levels in nonsmokers are usually less than 1 percent, while those in smokers average around 4 percent and may exceed 15 percent (4, 20, 52). Heavy smokers and those who inhale show the highest carboxyhemoglobin levels (20).

(a) The blood levels of carboxyhemoglobin cited in this paragraph do not represent the values reported in the literature. For nonsmokers the level is not usually less than 1%. In the 26 investigations reported, the overall mean for 1,662 subjects was 1.45% (see pages 32 and 33). For smokers the average is not 4%. The 30 investigations reported in the literature have an overall mean of 3.76% for 2,054 subjects. Values above 15% are very rare and are probably the result of an error in the analysis (see pages 12-15).

b/ Haebisch (24) found that a smoker with a daily consumption of 35 to 40 cigarettes easily attains and maintains for hours an alveolar CO concentration of 50 p.p.m., which reaches or exceeds legally-established ambient air quality standards (11, 18, 33, 24).

Cohen, et al. (13) and Arenow, et al. (2), have shown that there is no significant difference in mean expired air carbon monoxide levels after patients have smoked tobacco or lettuce leaf cigarettes. Although pipe and cigar smokers in the United States are reported to have lower exposure to CO than cigarette smokers (20), CO intoxication has been reported in cigar smokers (25).

(b) The observation of Haebisch (1970) is an isolated one. It should be noted that his value of 50 ppm carbon monoxide in alveolar air is 2 to 3 times greater than that reported by Jongbloed (1939) and Ringold et al (1962) (see page 19).

c/ CO exerts its adverse effects on the cardiovascular system of smokers through one or more of the following mechanisms: (a) reduction of the amount of hemoglobin available for oxygen transport; (b) shift of the oxygen-hemoglobin dissociation curve to the left with consequent interference in oxygen release at the tissue level; and (c) induction of arterial hypoxemia. CO may interfere with the homeostatic mechanism by which 2,3-DPG controls the affinity of hemoglobin for oxygen (56). CO has also been implicated in experimental atherogenesis in animals (56).

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(c) The list of 3 mechanisms actually represents one, which causes the formation of carboxyhemoglobin. Item (c), hypoxemia, meaning low oxygen tension, is not correct. There is low oxygen content but normal tension.

Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000

Commentary (6) National Clearinghouse, Cont.

Ayres, et al. (7) recently studied 41 patients during diagnostic cardiac catheterization, at which time they inhaled either 5 percent or .1 percent CO. Arterial and mixed venous oxygen tensions were decreased by administration of either concentration. In patients with CHD, coronary artery O_2 extraction decreased 7.9 percent after inhalation of .1 percent CO and 30.5 percent after inhalation of 5 percent CO. Some of the patients with CHD experienced changes in lactate and pyruvate metabolism indicative of inadequate myocardial oxygenation. The higher level of CO inhalation in this experiment is comparable to that experienced intermittently by cigarette smokers.

(d) The work of Ayres et al (1970) is based on a non-steady state and is commented upon elsewhere (see page 148).

Brewer and his colleagues (11) investigated cigarette smoking as a cause of hypoxemia in residents of Leadville, Colorado, at an altitude of 3,100 meters. The arterial pO_2 of 8 smokers was significantly lower ($P < .05$) than that of 12 nonsmokers, but this was reversible upon cessation of smoking. They concluded that the adverse effect of cigarette smoking on O_2 transport may be especially pronounced at high altitude and may restrict an individual's ability to adapt to reduced O_2 tensions (11, 12).

(e) The statement of the results of Brewer et al (1970, 1971) is incomplete. It should be added that the difference in oxygen tension between smokers and nonsmokers is small, amouting to 5 mm for pO_2. More important is the fact that the oxygen saturation for smokers is 74% and is higher than that of the nonsmoking individual (68%). The shift of the oxygen dissociation curve to the left in the blood of smokers accounts for higher oxygen saturation. Therefore, although oxygen tension is reduced, the saturation is higher for smokers. A paragraph from Brewer et al (1971) is quoted below.

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In the course of our smoking experiments we determined the CO content of the air in our 15 cu m exposure chamber (with approximately one air change/hour) and we found that the CO rose to approximately 20 ppm following the smoking of seven cigarettes in an hour. Particulate matter was 3 mg/cu m at the end of the hour. We also measured the concentrations of CO passing across the face of an observer who sat next to a subject for the ten minutes during which a cigarette was smoked. The air was sampled through a tube strapped to the observer's face, and it can be seen from FIGURE 9 that transient peaks of up to 90 ppm were measured.

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→ TO P. 134

Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000

Commentary (6) National Clearinghouse, Cont.

Kjeldsen (31, 32) examined 998 industrial workers, about one-half of whom were tobacco workers. Fifty-nine cases of arteriosclerosis were documented by such clinical symptoms as angina pectoris and intermittent claudication or by a previous history of myocardial infarction. While 20.9 percent of the 934 "control" individuals were nonsmokers, only 2 (3.4 percent) of the 59 patients with arteriosclerosis were nonsmokers. A significantly higher percentage of diseased workers were heavy smokers and inhaled the smoke.

The diseased smokers had significantly higher carboxyhemoglobin and serum cholesterol levels than either smoking or nonsmoking control patients. This was true after standardizing for differences in levels of smoking between controls and diseased patients. As expected, there was a gradient in carboxyhemoglobin levels from lower levels in light smokers to higher levels in heavy smokers (table 4).

TABLE 4.—*Average values of carboxyhemoglobin and serum cholesterol in Danish smokers and nonsmokers in control group and group of patients with arteriosclerotic cardiovascular disease.*

Smoking category	Carboxyhemoglobin (asturation percentage)			Serum cholesterol (mg/100 ml)		
	controls M±S.D.	patients M±S.D.	significance	controls M±S.D.	patients M±S.D.	significance
Smokers	4.2±3.1 (738)[a]	7.0±3.7 (57)	$p<0.001$ $t=5.52$	247±44 (738)	290±33 (57)	$p<0.001$ $t=4.89$
Nonsmokers	0.4±0.9 (196)	0.5±0.7 (2)	n.s. $t=0.16$	236±49 (196)	284±56 (2)	$p<0.02$ $t=2.32$
Light smokers	2.5±2.5 (121)	3.7±2.5 (3)	n.s. $t=0.76$	245±38 (121)	279±67 (3)	n.s. $t=1.45$
Moderate smokers	4.1±3.0 (463)	7.3±3.6 (34)	$p<0.001$ $t=4.95$	246±45 (463)	286±50 (34)	$p<0.001$ $t=4.52$
Heavy smokers	5.7±3.0 (154)	7.0±4.0 (20)	n.s. $t=1.45$	253±45 (154)	298±53 (20)	$p<0.05$ $t=2.18$

p = Probability that difference is not due to chance.
t = Student's t calculation.
n.s. = not significant.
[a] The number of subjects in each category is enclosed in parentheses beneath the mean (M) and standard deviation (S.D.).
SOURCE: Kjeldsen, K. (31).

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Kjeldsen also observed that the COHb levels of 8 to 19 percent seen in 40 percent of the patients with arteriosclerosis were of the same magnitude as those provoking experimental atherosclerosis and cardiac necrosis in animals.

(f) The observations of Kjeldsen (1969, 1970) have not been confirmed by others. It should be stated that Prerovska and Drdkova (1967, 1971) completed a retrospective examination of individuals who had been exposed to an environment of up to 1,000 ppm for an average duration of 10.5 years. There was no early development of arteriosclerosis.

Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000

THE EXTENT TO WHICH THE COMPONENTS OF CIGARETTE SMOKE CONTAMINATE THE ATMOSPHERE AND ARE ABSORBED BY THE NONSMOKER

Theoretical models of this contamination have been constructed. Owens and Rossano (*44*) have noted that most popular cigarettes release into the atmosphere approximately 70 mg. of dry particulate matter (about 60 mg. in the sidestream and slightly over 20 mg. in the mainstream, about one-half of the latter being absorbed by the smoker and one-half expelled into the ambient air) and 23 mg. carbon monoxide per cigarette. This material adds to the cleaning problem of the air of any enclosed space and contributes to residual odors. In a recent study of particulate matter filtration in domestic premises (*35*), the authors observed that the smoking of one cigar completely overcame the effect of an electrostatic filtration device for one hour.

Atmospheric pollutants caused by smoking are derived from two major sources: mainstream and sidestream smoke. Mainstream smoke emerges from the tobacco product through the mouthpiece during puffing, whereas sidestream smoke comes from the burning cone and from the mouthpiece during puff intermissions (*60*). The tobacco smoke released into the atmosphere consists of all the sidestream smoke as well as that part of the mainstream smoke which has been either held in the smoker's mouth or taken into his lungs and then expelled. The actual amount of material to which individuals are exposed in the presence of smokers depends upon the amount of smoke produced, the depth of inhalation on the part of the smoker, the ventilation available for the removal or dispersion of the smoke, and the proximity of the individual to the smoker. The length of time of exposure to these pollutants is extremely important in determining how much is absorbed into the body. The pattern of smoking influences the amount produced by altering the content of the exhaled smoke. As shown by Dalhamn, et al. (*10, 11*), mouth absorption removes approximately 60 percent of the water-soluble volatile components (e.g., acetaldehyde), 20 percent of the nonwater-soluble volatile components (e.g., isoprene), 16 percent of the particulate matter, and only three percent of the carbon monoxide. Thus, the smoker who does not inhale "filters" a portion of the smoke components in his mouth before expelling them into the ambient air. On the other hand, the lungs retain from 86 to 99 percent of the volatile and particulate substances and approximately 54 percent of the carbon monoxide inhaled. Hence, the inhaling smoker "filters" the mainstream smoke rather effectively before expelling it into the ambient air. A factor which has apparently not been investigated is the difference in the smokers' "filtration" of mainstream smoke when the smoke is exhaled through the nose instead of the mouth.

Thus, the nonsmoker breathes smoke-containing air composed of sidestream smoke and mainstream smoke exhaled by smokers. The inhaling smoker receives nearly the full amount of mainstream smoke as well as a portion of sidestream smoke and smoke exhaled by himself and other smokers. The smoker who does not inhale receives those compounds which are absorbed from the mainstream smoke in his mouth, as well as absorbing the sidestream smoke and the smoke exhaled by himself and other smokers contained in the air he breathes.

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Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000

Commentary (6) National Clearinghouse, Cont.

Since pipe and cigar smokers inhale less commonly than do cigarette smokers, their contribution to the substances in the air breathed in exposure to smoke pollutants consists of a composite of sidestream smoke and relatively unfiltered mainstream smoke which has been held in the mouth and then expelled.

The actual effluents in the mainstream and sidestream cigarette smoke have been considered by Pascasio, et al. (*45*) and Scassellati Sforzolini and colleagues (*50, 51*). These authors stated that "tar" and nicotine levels in sidestream smoke may be significantly higher than those of mainstream smoke and may be harmful to the nonsmoker. Actual volume measurements were not reported, however.

Actual measurements of the contamination due to cigarette smoking have been carried out by a number of research groups. A recent, well-controlled study by Harke (*24*) involved the smoking of 42 cigarettes in 16 to 18 minutes using German blend cigarettes of 85 mm. length, 18 mm. filter, and smoked to a 25 mm. butt length in a room with a volume of 57 cubic meters (approximately the equivalent of a room with a 10-foot ceiling and dimensions of 12 by 14 feet). The author observed that in the absence of ventilation the atmosphere contained up to 50 p.p.m. carbon monoxide and .57 mg./m.^{3} nicotine. With substantial ventilation, these levels fell significantly (to approximately 10 p.p.m. carbon monoxide and .10 mg./m.^{3} nicotine). He also found that cigar smoke (9 cigars of Clear Sumatra tobacco smoked in 30 to 35 minutes) produced similar amounts of contamination while pipe smoke (2 grams of Navy type medium cut tobacco smoked as eight pipefuls in 35 to 40 minutes) produced much less. Other authors have made similar measurements. Galuskinova (*20*) found that 3,4-benzpyrene levels in a smoky restaurant were from 2.82 to 14.4 mg./100 m.^{3} as compared to outside atmospheric levels of 0.23 to 0.46 mg./100 m.^{3}, although burning of food particles may have contributed to the presence of 3,4-benzpyrene in this setting. Kotin and Falk (*33*) have shown that sidestream cigarette smoke condensate may contain more than three times as much benzo(a)pyrene as mainstream smoke. Srch (*55*) observed that the smoking of 10 cigarettes to a 5 mm. butt length in an enclosed car of 2.09 m.^{3} volume produced carbon monoxide levels up to 90 p.p.m. Lawther and Commins (*34*), working with a ventilated chamber, found levels of up to 20 p.p.m. of carbon monoxide after seven cigarettes were smoked in one hour; however, peaks of up to 90 p.p.m. were recorded at the seat next to the smoker. Coburn, et al. (*9*) recorded levels of 20 p.p.m. of carbon monoxide in a small conference room after 10 cigarettes were "burned." Harmsen and Effenberger (*25*) reported up to 80 p.p.m. of carbon monoxide in an enclosed 98 m.^{3} room (approximately the equivalent of a room with a 10-foot ceiling and dimensions of 18 by 20 feet) in which 62 cigarettes had been smoked in two hours.

Another set of contaminants probably present in a tobacco smoke-polluted atmosphere are the oxides of nitrogen. These, specifically NO and NO_2, have been shown to be present in tobacco smoke although the type most likely to be present in the atmosphere is NO_2. No measurements have been reported of the amount of NO_2 in smoke-filled rooms. The importance of obtaining and evaluating this information is stressed by the results of Freeman and Haydon and

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Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000

their colleagues (*17, 18, 19, 27, 28*) and of Blair, et al. (*5*) who observed bronchial and pulmonary parenchymal lesions in rodents continuously exposed to low levels of NO_2.

Other experimenters have measured carboxyhemoglobin (COHb) levels in nonsmokers exposed to cigarette smoke pollutants. Srch (*55*) observed that the COHb level in two nonsmokers rose from 2 to 5 percent (that of smokers from 5 to 10 percent) when seated in the cigarette-smoke contaminated car mentioned above (exposure to 90 p.p.m.). Harke (*24*) reported that when seven nonsmokers were exposed for approximately 90 minutes to a "smoked" room containing 30 p.p.m. of CO there was a rise in COHb from a mean of 0.9 percent to 2.0 percent. In 11 smokers subjected to the same conditions, COHb rose from a mean of 3.3 percent to 7.5 percent. With improved ventilation of the experimental room, the COHb level decreased significantly.

The CO exposures and COHb levels reported above closely approximate the results obtained following experimental chamber exposure of humans to various levels of CO. The uptake of CO by the person depends on, among other parameters: CO concentration, previous COHb level, the level of activity, and the person's state of health. Equilibrium between CO concentration in the lung and in the blood requires over 12 hours exposure. However, as may be noted in table 1, reproduced from Stewart, et al. (*56*) and derived from measures of COHb in young sedentary males who were not smoking, over half of the equilibrium COHb level is reached within three to four hours of the onset of exposure. The equilibrium value associated with 100 p.p.m. is approximately 14 to 15 percent COHb. Exposure to 100 p.p.m. in the nonsmoker can lead to 3.0 percent of COHb within 60 minutes and 6.0 percent in two hours (*16*). Of equal significance is that COHb has a half-life of at least three to four hours in the body. As shown in table 1, the COHb level fell only to 2.7 percent in the two hours following cessation of exposure to 50 p.p.m. from the end exposure level of 3.7 percent. This lengthy half-life extends the period of effect of exposure to CO and provides for a buildup of COHb concentration from fresh exposures.

TABLE 1.—*Percent of COHb during and following exposure to 50 p.p.m. of CO.*

Time during exposure	Mean	Range	Number of subjects
Preexposure	0.7	0.4–1.5	11
30 minutes	1.3	1.3	3
1 hour	2.1	1.9–2.7	11
3 hours	3.8	3.6–4.2	10
6 hours	5.1	4.9–5.5	5
8 hours	5.9	5.4–6.2	5
12 hours	7.0	6.5–7.9	3
15 ½ hours	7.6	7.2–8.2	3
22 hours	8.5	8.1–8.7	3
24 hours	7.9	7.6–8.2	3
Time without exposure after 1 hour of exposure			
30 minutes	1.8	1.8	3
1 hour	1.7	1.6–1.8	3
2 hours	1.5	1.4–1.5	3
5 hours	1.1	1.0–1.1	2

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Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000

Commentary (6) National Clearinghouse, Cont.

Time without exposure after 3 hours of exposure			
30 minutes	3.7	3.4–3.9	3
1 hour	3.3	2.7–3.8	3
2 hours	2.7	2.3–3.0	3
Time without exposure after 8 hours of exposure			
30 minutes	5.6	5.1–5.9	3
1 hour	5.1	4.8–5.4	3
1 ¾ hours	4.0	—	—
11 hours	1.5	1.4–1.7	3
Time without exposure after 24 hours of exposure			
30 minutes	7.5	7.2–7.8	3
1 hour	6.7	6.4–7.1	3
2 hours	5.8	5.6–6.2	3

(g) This section includes an incomplete citation of work by the various investigators. For instance, Harke's conclusion that "it is unlikely to find non-smokers in a room absorbing a significant amount of cigarette smoke" is not mentioned at all. The blood levels that show low absoprtion are mentioned two paragraphs later. The passive smoker had a blood level of 2% carboxyhemoglobin, an increase of 1.1% over the control level (see page 25).

(h) Srch (1967) not only smoked "in an enclosed car" but also had the motor running in a closed garage. The high levels of carbon monoxide arise largely from automobile exhaust and this is not stated in the quotation (see page 36).

(i) Lowther and Cummins (1970) worked with a ventilated chamber. Examination of the original article reveals that the chamber is 15 cu m, with approximately 1 air change per hour. The high values for carbon monoxide in the air are understandable (see paragraph from article).

Data from 2 representative oxygen tensions are shown in Figure 5 and Table 4. Although there is overlap, the mean saturation values of the normal smokers and the polycythemic smokers are significantly higher than that of non-smoking normals at one of the two oxygen tensions (Table 5). This means that, on the average, the oxygen dissociation curve of smokers in Leadville is left-shifted compared to non-smokers. There was no significant difference between the position of the curve in normal smokers and polycythemic smokers at either oxygen tension.

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Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000

Commentary (6) National Clearinghouse, Cont.

THE EFFECTS OF LOW LEVELS OF CARBON MONOXIDE ON HUMAN HEALTH

The data on the effect of low levels of carbon monoxide on human psychological and physiological function have been summarized in two recent publications (8, 58).

There is presently much discussion as to the physiologic and psychophysiologic effects of exposure to levels of CO approximating 50 to 100 p.p.m. Beard and Grandstaff (4) observed that exposure to 50 p.p.m. of CO for from 27 to 90 minutes altered auditory discrimination, visual acuity, and the ability to distinguish relative brightness. McFarland (37) observed that COHb levels of 4 to 5 percent caused visual threshold impairment. Ray and Rockwell (48), reporting on a study of the driving ability of three subjects under varying CO exposure, observed that the presence of 10 percent COHb was associated with increased response time for taillight discrimination and increased variance in distance estimation. Schulte (52) observed that increased errors in cognitive and choice discrimination tests were manifest at levels of COHb as low as 3 percent. Chevalier, et al. (7) have also observed that levels of 4 percent COHb in nonsmokers are associated with an increase in oxygen debt formation with exercise similar to that seen in smokers.

On the other hand, other investigators utilizing complex psychomotor tasks in men and monkeys have observed no decrement in function upon exposures to CO at 50 to 250 p.p.m. (2, 3, 23, 41, 56).

(j) The investigations that concentration of 50 to 250 ppm carbon monoxide does not influence the central nervous system are not described in detail. There are many other reports which are also negative (see Pages 88-90).

Animals exposed to low levels of CO (50 to 100 p.p.m.) continuously for weeks have shown varying degrees of cardiac and cerebral damage similar to that produced by hypoxia (21, 47, 57).

Finally, the possible effects of exposure to 50–100 p.p.m. CO on patients with coronary heart disease (CHD) were investigated by Ayres, et al. (1) who observed a decrease in arterial and mixed venous oxygen tensions with COHb saturations of 5 percent. Certain patients with CHD developed altered lactate and pyruvate metabolism with COHb levels of 5 to 10 percent suggesting myocardial hypoxia.

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(k) The cited work of Ayres et al (1970) was performed in a non-steady state with inhalation of 5% carbon monoxide. The validity of these observations is discussed elsewhere in this commentary (see page 148).

Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000

Commentary (6) National Clearinghouse, Cont.

The evidence concerning the effect of low levels of carbon monoxide has recently been reviewed and evaluated by the National Air Quality Criteria Committee of the National Air Pollution Control Administration (55). The following is taken from the published conclusions of the Advisory Committee (also see table 2):

> "Experimental exposure of nonsmokers to 58 mg/m³ (50 ppm) for 90 minutes has been associated with impairment in time-interval discrimination.... This exposure will produce an increase of about 2 percent COHb in the blood. This same increase in blood COHb will occur with continuous exposure to 12 to 17 mg/m³ (10 to 15 ppm) for 8 or more hours....
>
> "Experimental exposure to CO concentrations sufficient to produce blood COHb levels of about 5 percent (a level producible by exposure to about 35 mg/m³ for 8 or more hours) has provided in some instances evidence of impaired performance on certain other psychomotor tests, and an impairment in visual discrimination....
>
> "Experimental exposure to CO concentrations sufficient to produce blood COHb levels above 5 percent (a level producible by exposure to 35 mg/m³ or more for 8 or more hours) has provided evidence of physiologic stress in patients with heart disease...."

The levels of carbon monoxide found to be present in "smoked" rooms (20 to 80 p.p.m.) are similar to the levels (30 to 50 p.p.m.) which the Advisory Committee has concluded are associated with adverse health effects:

> "An exposure of 8 or more hours to a carbon monoxide concentration of 12 to 17 mg/m³ (10 to 15 ppm) will produce a blood carboxyhemoglobin level of 2.0 to 2.5 percent in nonsmokers. This level of blood carboxyhemoglobin has been associated with adverse health effects as manifested by impaired time interval discrimination. Evidence also indicates that an exposure of 8 or more hours to a CO concentration of 35 mg/m³ (30 ppm) will produce blood carboxyhemoglobin levels of about 5 percent in nonsmokers. Adverse health effects as manifested by impaired performance on certain other psychomotor tests have been associated with this blood carboxyhemoglobin level, and above this level there is evidence of physiologic stress in patients with heart disease."

These levels of CO are also similar to that set as the time-weighted occupational Threshold Limit Value of 50 p.p.m. for a 40-hour week (five 8-hour days) which has been in effect in the United States for the past several years (15). A further reduction in this limit to 25 p.p.m. is now under consideration. These levels of CO exceed those recently set by the Environmental Protection Agency as the national primary and secondary ambient air quality standards for CO (12). These standards are:

(a) 10 milligrams per cubic meter (9 p.p.m.)—maximum 8-hours concentration not to be exceeded more than once per year.

(b) 40 milligrams per cubic meter (35 p.p.m.)—maximum 1-hour concentration not to be exceeded more than once per year.

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Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000

TABLE 2.—*Effects of carbon monoxide.*

Environmental conditions	Effect	Comment
58 mg./m.³ (50 p.p.m.) for 90 minutes	Impairment of time-interval discrimination in non-smokers.	Blood COHb levels not available, but anticipated to be about 2.5 percent. Similar blood COHb levels expected from exposure to 10 to 17 mg./m.³ (10 to 15 p.p.m.) for 8 or more hours.
115 mg./m.³ (100 p.p.m.) intermittently through a facial mask	Impairment in performance of some psychomotor tests at a COHb level of 5 percent.	Similar results may have been observed at lower COHb levels, but blood measurements were not accurate.
High concentrations of CO were administered for 30 to 120 seconds, and then 10 minutes was allowed for washout of alveolar CO before blood COHb was measured.	Exposure sufficient to produce blood COHb levels above 5 percent has been shown to place a physiologic stress on patients with heart disease.	Data rely on COHb levels produced rapidly after short exposure to high levels of CO; this is not necessarily comparable to exposure over a longer time period or under equilibrium conditions.

SOURCE: Adapted from U.S. Public Health Service, Air Quality Criteria for Carbon Monoxide. Washington, D.C., U.S. Department of Health, Education, and Welfare (53).

(1) The remainder of this section quotes the decision by the National Air Pollution Control Administration, which was drafted mainly for industrial exposures lasting 8 hours. The criteria used by this agency do not apply to brief exposures to cigarette smoke.

ALLERGIC AND IRRITATIVE REACTIONS TO CIGARETTE SMOKE AMONG NONSMOKERS

(A more detailed discussion of this subject is presented in the Allergy chapter of this report.)

Several investigators have reported on the discomfort and symptoms experienced by both allergic and nonallergic individuals upon exposure to tobacco smoke. Johansson and Ronge (*31*, *32*) in 1965 and 1966 have observed that the acute irritation experienced by nonsmokers in the presence of tobacco smoke is maximal in warm, dry air and that nonsmokers experience more nasal irritation than ocular irritation as compared with smokers exposed to similar amounts of smoke in the atmosphere. Speer (*54*) studied the reactions of 441 nonsmokers divided into two groups, one composed of individuals with a history of allergic reactions and the other of individuals without such a history. The allergic group underwent skin testing for the presence of sensitivity to tobacco extract while the "nonallergic" group was determined solely by questionnaire concerning subjective allergic responses. Approximately 70 percent of both groups experienced eye irritation while other symptoms differed in their frequency from group to group (nasal symptoms

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Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000

allergic 67 percent, "nonallergic" 23 percent; headache: allergic 46 percent, "nonallergic" 31 percent; cough: allergic 46 percent, "nonallergic" 25 percent; and wheezing: allergic 22 percent, "nonallergic" 4 percent). Thus, a significant proportion of nonsmoking individuals report discomfort and respiratory symptoms on exposure to tobacco smoke.

Other authors have attempted to separate out those patients who may have specific allergies to smoke. Zuskman (*61*) found that in a random series of 200 atopic patients 16 percent were clinically sensitive to tobacco smoke, and that a majority of these were aided by desensitization therapy. In an earlier study, Pipes (*46*) observed that 13 percent of 229 patients with respiratory allergy showed positive skin tests to tobacco smoke. Savel (*49*) has recently reported on eight nonsmokers observed to be clinically hypersensitive to tobacco smoke. After *in vitro* incubation of their lymphocytes with cigarette smoke, increased incorporation of tritiated thymidine was recorded; similar exposure of the lymphocytes of those not sensitive resulted in depression of tritiated thymidine uptake.

Luquette, et al. (*39*) have recently reported on the immediate effects of exposure to cigarette smoke in school-age children. They observed that heart rate and blood pressure rose with such exposure, although questions remain about the adequacy of their controls and the manner in which the experimental situation may have excited the subjects. Finally, Cameron, et al. (*6*) observed that acute respiratory illnesses were more frequent among children from homes in which the parents smoked than among children of nonsmoking parents. The meaning of these results is uncertain since smoking by the children was not considered and the level of exposure to cigarette smoke in their homes was not measured. Shy, et al. (*53*) in a study of second grade Chattanooga school children failed to demonstrate a relationship between parental smoking habits and the respiratory illness rates of their children.

(m) This section on allergic reactions refers to components of cigarette smoke other than carbon monoxide. There is no case of reported allergy to carbon monoxide.

THE KNOWN HARMFUL EFFECTS OF THE PASSIVE INHALATION OF CIGARETTE SMOKE IN ANIMALS

(n) A number of investigators have studied the effects of the passive inhalation of high concentrations of cigarette smoke on the pulmonary parenchyma and tracheobronchial tree of animals. The results of these investigations are listed in detail in the recent report to Congress, "The Health Consequences of Smoking," (*59*) in table 9 of the Bronchopulmonary chapter, and table 16 of the Cancer chapter.

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The pathologic changes observed in the respiratory tract of the animals included parenchymal disruption, bronchitis, tracheobronchial epithelial dysplasia and metaplasia, and pulmonary adenomatous tumor formation. Leuchtenberger, et al. (*36*) exposed 151 mice to the smoke of from 25 to 1,526 cigarettes over a period of 1 to 23 months and observed that 20 percent of the animals developed severe bronchitis with atypism. Working with 30 control rabbits exposed to up to 20 cigarettes per day for two to five years, Holland, et al. (*30*) observed increased focal and generalized hyperplasia of the bronchial epithelium and generalized emphysema in the exposed rabbits. Hernandez, et al. (*29*) observed significantly more pulmonary parenchymal disruption in adult greyhound dogs exposed to cigarette smoke 10 times per week for approximately one year than in nonexposed control animals.

Lorenz, et al. (*38*) observed no increase in respiratory tract tumor formation above that seen in controls in 97 Strain A mice exposed to cigarette smoke for up to 693 hours. Essenberg (*15*), however, exposed Strain A mice to cigarette smoke for 12 hours a day for up to one year and observed significantly more papillary adenocarcinomas in the exposed than in the control group. An increased percentage of hybrid mice were found by Mühlbock (*42*) to have alveolar carcinomas among the experimental group exposed to smoke for two hours a day for up to 684 days when compared with a nonexposed group. Similarly, Guerin (*22*) observed that 5.1 percent of rats exposed to cigarette smoke for 45 minutes a day for two to six months showed pulmonary tumors compared to 2.4 percent of the control mice.

Leuchtenberger, et al. (*37*), working with 400 female CF, mice, observed only a slight increase in the presence of pulmonary adenomatous tumors among those exposed to cigarette smoke compared with those in the control group. The authors commented that the presence of tumors showed an age relationship independent of smoking exposure. Otto (*43*) found that 11 percent of a group of albino mice exposed to 12 cigarettes a day for up to 24 months showed pulmonary adenomas as compared with five percent of the control non-exposed group. Dontenwill and Wiebecke (*12*) found that increasing the exposure of golden hamsters to up to four cigarettes a day for up to two years was associated with an increasing percentage of animals showing desquamative metaplasia and bronchial papillary metaplasia. Harris and Negroni (*26*) exposed 200 C57BL mice to cigarette smoke for 20 minutes a day every other day for life and found eight adenocarcinomas as compared to none in the control group.

Because the damage observed in these experiments was seen after prolonged exposure to high concentrations of cigarette smoke, and because the comparability of animal exposure to smoke with that of human exposure in smoke-filled rooms is unknown, it is presently impossible to be certain from animal experimentation about the extent of the damage that may occur during long-term intermittent exposure to lower concentrations.

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Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000

Commentary (6) National Clearinghouse, Cont.

SUMMARY

1. An atmosphere contaminated with tobacco smoke can contribute to the discomfort of many individuals.

2. The level of carbon monoxide attained in experiments using rooms filled with tobacco smoke has been shown to equal, and at times to exceed, the legal limits for maximum air pollution permitted for ambient air quality in several localities and can also exceed the occupational Threshold Limit Value for a normal work period presently in effect for the United States as a whole. The presence of such levels indicates that the effect of exposure to carbon monoxide may on occasion, depending upon the length of exposure, be sufficient to be harmful to the health of an exposed person. This would be particularly significant for people who are already suffering from chronic bronchopulmonary disease and coronary heart disease.

3. Other components of tobacco smoke, such as particulate matter and the oxides of nitrogen, have been shown in various concentrations to adversely affect animal pulmonary and cardiac structure and function. The extent of the contributions of these substances to illness in humans exposed to the concentrations present in an atmosphere contaminated with tobacco smoke is not presently known.

(n) The experiments on animals were not controlled and there is no reported concentration of carbon monoxide. It is not possible to relate the observations on animals to humans unless the concentration of cigarette smoke is known.

1005051204

Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000

(7) ABELSON P H : A damaging source of air pollution. Science 158: 1527, 1967.

> One of the toxic products of the automobile is carbon monoxide. Exposure for 1 hour to a concentration of this gas of 120 parts per million causes inactivation of about 5 percent of the body's hemoglobin and commonly leads to dizziness, headache, and lassitude. Concentrations of carbon monoxide as high as 100 ppm often occur in garages, in tunnels, and behind automobiles. Such concentrations are tiny in comparison with those (42,000 ppm) found in cigarette smoke. The smoker survives because most of the time he breathes air not so heavily polluted. However, in a poorly ventilated, smoke-filled room, concentrations of carbon monoxide can easily reach several hundred parts per million, thus exposing smokers and nonsmokers present to a toxic hazard.

In this article, the comparison of concentration of carbon monoxide is as follows: 100 ppm for garages and tunnels and 42,000 ppm in cigarette smoke. The latter represents 4.2 carbon monoxide in pure cigarette smoke. This concentration is not inhaled continuously, but is diluted by air in the lungs at the time of inhalation of cigarette smoke. After exhalation, atmospheric air enters to replace the cigarette smoke. Ringold et al. (1962) analyzed the expired air to determine the integrated concentration of carbon monoxide therein: that of heavy smokers had a concentration of 16.4 ppm, light smokers 7.7 ppm, and nonsmokers 0.08 ppm (see page 19).

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Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000

(8) ANON : Carbon monoxide. Am Industr Hyg Ass J 26: 431-4, 1965.

> The blood of cigarette smokers will contain from 2% to 10% carboxyhemoglobin and nonexposed adults will show a normal average background of 1% carboxyhemoglobin.[4]

The blood volumes for smokers are overestimated and those for nonsmokers underestimated. The overall mean value reported in 30 investigations is 3.76% for smokers (see page 12). The overall mean value recorded in 26 investigations is 1.45% for nonsmokers.

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Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000

(9) ANON : Carbon monoxide poisoning - a timely warning. New England J Med 278: 849-50, 1968.

> The cigarette is another producer of carbon monoxide. Heavy cigarette smokers may have as much as 10 per cent carbon monoxide hemoglobin in their blood. Such levels may not be sufficient to cause impairment at sea level but will be enough to produce changes at altitudes of 8000 to 10,000 feet. A recent article has demonstrated behavioral impairment associated with small doses of carbon monoxide[3] — levels of exposure in the range accepted as tolerable in industry. The results indicate that impairment of cerebral function can occur at extremely low levels (50 to 250 ppm) during exposures of half an hour to two and a half hours. Further support for central-nervous-system effects comes from the observation that low levels of carbon monoxide hemoglobin can significantly raise the threshold of light sensitivity of the eye.[4]

That heavy cigarette smoking may cause as much as 10% carboxyhemoglobin in the blood is rare. Barach et al (1941) measured the peak levels in the blood of 18 subjects who smoked 20 cigarettes daily and noted a mean level of 5.7%, with a range of 2.2% to 12.3%. Fabre et al (1951), in a group of 5 subjects smoking 24 cigarettes, reported a mean level of 4.85%, which represented an increase of 2.7% over the level prior to smoking (see page 21).

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Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000

(10) ANON : Warning: Cigarettes are dangerous to your health. American Cancer Society. Med Bull Montgomery County Med Soc 24: 45-7, 1968.

> Some of these carcinogens may be as simple carbon monoxide — CO — one of the standard by-products of automobile exhaust. Colorless and odorless, this compound of carbon and oxygen is fatal when as little as one-tenth of one per-cent is breathed in continuously; in minute quantities and repeated doses, it can also be a slow cause of death as a producer of cancer.

Carbon monoxide is not a carcinogen. Carbon monoxide has been tested in mice with tumors induced by chemicals. Carbon monoxide did not influence the rate of tumor growth.

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Source: https://www.industrydocuments.ucsf.edu/docs/nfmk0000